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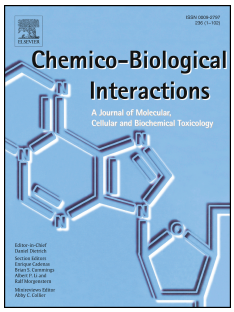

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PII: S0009-2797(20)30486-5

DOI: https://doi.org/10.1016/j.cbi.2020.109125

Reference: CBI 109125

To appear in: *Chemico-Biological Interactions*

Received Date: 24 March 2020

Revised Date: 16 April 2020

Accepted Date: 29 April 2020

Please cite this article as: P. Prasher, M. Sharma, M. Mehta, K.R. Paudel, S. Satija, D.K. Chellappan, H. Dureja, G. Gupta, M.M. Tambuwala, P. Negi, P.R. Wich, N. Hansbro, P.M. Hansbro, K. Dua, Plants derived therapeutic strategies targeting chronic respiratory diseases: Chemical and immunological perspective, *Chemico-Biological Interactions* (2020), doi: https://doi.org/10.1016/j.cbi.2020.109125.

Plants derived therapeutic strategies targeting chronic respiratory diseases: Chemical and Immunological Perspective

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Abstract

The apparent predicament of the representative chemotherapy for managing respiratory distress calls for an obligatory deliberation for identifying the pharmaceuticals that effectively counter the contemporary intricacies associated with target disease. Multiple, complex regulatory pathways manifest chronic pulmonary disorders, which require chemotherapeutics that produce composite inhibitory effect. The cost effective natural product based molecules hold a high fervor to meet the prospects posed by current respiratory-distress therapy by sparing the tedious drug design and development archetypes, present a robust standing for the possible replacement of the fading practice of poly-pharmacology, and ensure the subversion of a potential disease relapse. This study summarizes the experimental evidences on natural products moieties and their components that illustrates therapeutic efficacy on respiratory disorders.

Keywords: COPD; natural products; respiratory disorders; alkaloids; flavonoids

1. Introduction

The chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), pulmonary sarcoidosis, asthma, pneumoconiosis, and lung cancer pose major healthcare and economic strain across the globe. As per the annual report by World Health Organization (WHO) on 'The Global Impact of Respiratory Disease', COPD alone claims a global morbidity of 65 million, including 3 million annual mortalities. The figures for asthma further raise the alarm with 334 million people suffering from the disease, which includes 14% of children [1]. Notably, pneumonia; caused by bacteria *streptococcus pneumonia* raises the mortality rate among children below 5 years of age. Tuberculosis, a chronic respiratory ailment caused by bacteria *mycobacterium tuberculosis* affects 10 million people annually, out of which 1.4 million lose lives. In addition, lung cancer represents a fatal, yet most common neoplasm claiming roughly 2 million lives annually [2].

The pathophysiology of COPD manifests chronic inflammation in the lung parenchyma mediated by macrophages, neutrophils, and cytotoxic (CD8+) T lymphocytes. The subsequent fibrosis results in narrowing of small airways and obliteration of parenchyma by proteases. Reportedly, the development of COPD focused precision medicine faces considerable challenges due to dearth of animal models for preliminary drug testing, and due to a lack of information about the surrogate markers for monitoring the efficacy of rationally designed drugs [3]. Bronchial asthma, an inflammatory condition develops due to the abnormal activity of enzymes and prostanoids [4], coupled with oxidative stress in the airways resulting in hypertrophy and hyperplasia of bronchial smooth muscles, hyper-responsiveness and hypersecretion of mucins in the airway passages [5]. Besides the anti-asthma drugs targeting cysteinyl leukotrienes, immunoglobulin E, anticholinergics, and β-AR agonists, the contemporary chemotherapy

development efforts against asthma could not yield clinically efficacious results in the last 3 decades [6]. The emergence of multi-drug resistance microbial strains tainted the drug development efforts directed at pneumonia and tuberculosis [7], which are emerging as leading cause of excessive and unregulated antibiotic consumption [8]. Similarly, adenocarcinoma presents the recurring and most prevalent cancer type among the various lung cancer forms [9].

Various cell signaling pathway are involved in inflammatory and oxidative response, remodeling of extracellular matrix leading to asthma, COPD and pulmonary fibrosis whereas cell migration and proliferation pathway leading to lung cancer progression [10-13]. In asthma and COPD, oxidative stress leads to inflammation in airway by through redox sensitive transcription factor, nuclear factor (NF)-kappaB (NF-kB) pathway [14]. The activation NF-κB in cytoplasm and subsequent translocation to nucleus is induced by inflammatory cytokines such as interleukin (IL)-1β and tumour necrosis factor (TNF)-α whereas *via* activation of toll like receptors (TLRs) during pathogenic infections (bacterial or viral) [15]. Similarly, increase in transforming growth factor (TGF)-b by airway epithelial cells and inflammatory cells are involved in the pathogenesis of pulmonary fibrosis. High level of TGF-b results in activation, migration, and proliferation of resident fibroblasts. These fibroblasts can differentiation into activated myofibroblasts promoting abundant extracellular matrix (ECM) deposition and abnormal collagen build-up [16]. Likewise, activation of pathway such as epidermal growth factor receptor-tyrosine kinase, anaplastic lymphoma kinase (ALK), c-ros oncogene-1 (ROS1), programmed cell-death-1/program cell death ligand -1 (PD-1/PD-L1), mitogen activated protein kinases (MAPK), phosphoinositide 3-kinases (PI3Ks) are involved in migration and proliferation pathway leading to lung cancer progression [17-21].

Various natural compound are able to target the cell-signaling pathway showing beneficial activity against respiratory disease (Figure 1). The natural products containing alkaloids, flavonoids and terpenes serve as storehouse of essential chemotherapeutics [22-24], which produce desirable effects against chronic respiratory ailments (Table 1). These also prompt the development of novel drug systems by providing suitable pharmacophores for producing optimum effect against the target pathways associated with the manifestation of respiratory disorders [25]. This review presents a succinct discussion on the potential of natural product derived drugs based on alkaloids, flavones and terpenes for capping the conventional and emerging respiratory disorders.

Alkaloids

Lu *et al*. 2007; reported the medicinal properties of tetrahydroquinoline alkaloid '*Antidesmone*' (**1**, Figure 2) for the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), which represent prolonged inflammatory disorders instigated by membrane lipopolysaccharide (LPS) present on *gram-negative* bacteria, characterized by lung parenchymal injury and interstitial edema [26]. The microbial LPS instigate neutrophil infiltration, and trigger the production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), mitogen-activated protein kinase (MAPK) [27], cyclooxygenase-2 (COX-2) [28], interleukin-1β (IL-1β) [29], inducible nitric oxide synthase (iNOS) [30], nuclear factor-kappa B (NF-κβ) [31] and interleukin-6 (IL-6) [32] at the target site, thereby inducing acute lung injury.

Exposure with antidesmone significantly down-regulated MAPK and TNF-α signaling pathway and apparently lowered the expression of NF-κβ by offsetting the nuclear translocation of REL-associated protein p65, responsible for its activation [33]. Interestingly, the antidesmone exposure demonstrated significant inhibition of pulmonary myeloperoxidase (MPO), the

biomarker for accumulation of neutrophils in the morbid lungs [34], further validating the therapeutic privilege of the alkaloid.

Reportedly, cigarette smoke (CS) potentiates the redox imbalance by activating lung epithelial cells and macrophages, thereby resulting in chronic respiratory ailments [35]. The heightened oxidative stress caused by CS dissociates transcription factor Nrf2 from kelch-like ECH-associated protein 1 (Keap1) [36], eventually translocating into nucleus followed by binding to antioxidant response elements (ARE). These events regulate downstream gene expression for phase II detoxification enzymes such as glutamate cysteine ligase (GCL), glutathione S-transferase (GST), and heme oxygenase 1 (HO-1)[37] , that promote in maintaining cellular redox balance [38]. Therefore, Nrf2 signaling pathways present potential therapeutic target against the physiological redox imbalance [39].

Liu *et al*. 2020; investigated the therapeutic potential of six isosteroid alkaloids (**2-7**, Figure 2) obtained from *F. cirrhosa* bulbus against the CS induced oxidative stress in RAW264.7 macrophages. Reportedly, the identified six test alkaloids significantly attenuated the production of reactive oxygen species (ROS), upregulated the level of antioxidant molecule glutathione (GSH), and promoted the Nrf2 induced expression of HO-1 protein. Notably, the presence of glucoside moiety at C-3 position in alkaloid **5**, and absence of β-OH at C-17 position in alkaloid **6** resulted in higher GSH/GSSG ratio. Similarly, the presence of β-CH_3 substituent at C-20 position in alkaloid **3** favored its efficacy and tolerable cytotoxicity. The presence of –OH substitution at C-3 position in all the test alkaloids demonstrated a paramount importance for inducing HO-1 expression, which diminished in the presence of C=O group at the same position [40].

Zhao *et al*. 2017; investigated the curative effects and pharmacokinetics of alkaloids **8-11**, Figure 2, obtained from *A. scholaris* on ovalbumin induced airways allergic inflammatory model [41]. Exposure to the test alkaloids lowered the levels of leukocytes and eosinophils, further confirmed by histopathological analysis of lungs. Notably, the test alkaloids downregulated the secretion of proinflammatory cytokine IL-4, a key mediator of allergic responses eventually resulting in a significant reduction of pulmonary eosinophils, and balancing the rise of immunoglobulin E (IgE) in serum.

Importantly, the animal models administered with the test alkaloids 3 times a day demonstrated lower levels of eotaxin in the serum. Eotaxin overexpressed in the serum and airways of asthmatics serves as a biomarker for the pathogenesis of chronic asthma [42]. Therefore, its elimination from the systemic circulation in the morbid groups further validates the anti-asthma efficacy of test alkaloids. The administration of total alkaloids produced marked effect as compared to the single test alkaloid, hence confirming a synergistic effect. Moreover, these alkaloids proved useful for the treatment of post-infectious symptoms in animal models by mitigating the levels of inflammatory cytokines followed by down-regulation of the expression of IL-6. Histopathological examination of the morbid lungs further confirmed these observations [43]. Liu *et al*. 2015; isolated quinazoline alkaloids **12-14**, Figure 2, from the aerial parts of *Peganum harmala* L [44], and tested their antitussive, expectorant, and bronchodilating effects in animal models.

The alkaloids effectively lowered the symptoms associated with capsaicin induced acute pulmonary inflammation at doses 5, 15, and 45 mg/ kg, compared to codeine phosphate administered at 30 mg/ kg. The test alkaloids appreciably promoted expectorant activity as indicated by phenol red secretion in mice trachea, compared to the standard drug ammonium

chloride. Further, the bronchodilating test verified that the test alkaloids considerably prolonged the pre-convulsive times in animal models, superior to the standard drug aminophylline, thereby validating the potency of these alkaloids for treating bronchial asthma.

Alkaloids from *Cissampelos sympodialis* 'warifteine' (**15**, Figure 2) display notable efficacy in airway hyperreactivity in animal model of asthma [45]. Oral pretreatment of animal models with the test alkaloid warifteine significantly reduced the allergen induced airway hyperreactivity (AHR) to inhaled methacholine. Moreover, it also reduced the IL-13 levels in bronchoalveolar lavage, which serves as the key regulator of AHR [46]. The test alkaloid checked the ovalbumin (OVA)-induced eosinophil intrusion in the tissues, and downregulated the mucus production and subepithelial fibrosis. Further analysis of airway mucins by periodic acid-Schiff (PAS) staining revealed OVA induced metaplasia and mucus accumulation in animal models, which reduced significantly after warifteine administration.

Kim *et al*. 2015; reported attenuation of IL-4 and eotaxin-2 mediated eosinophilic airway inflammation in asthmatic animal models by the alkaloid 'chelidonine' (**16**, Figure 2) isolated from *Chelidonium majus* [47]. The test alkaloid significantly suppressed the level of eosinophils in the airways, in addition to downregulation of eotaxin-2, interleukins, and cytokines in the bronchoalveolar lavage fluid. Notably, chelidonine treated animal models exhibited considerable decrease of $CD4^+$ and $CD8^+$ T cells, $Gr\text{-}1^+$ /$CD11b^+$ and 351 $CD3/CCR3^+$ positive cells, which otherwise intensify inflammation process by secreting Th2 cytokines and degranulation of eosinophils [48]. Histological analysis suggested marked attenuation of OVA-induced eosinophil subversion, goblet cell hyperplasia, and accumulation of collagen in ling tissues in the presence of chelidonine. These findings validated the therapeutic potency of this alkaloid in the treatment of pathologic inflammatory disorders associated with respiratory airways.

Alkaloids **17** and **18** (Figure 2) obtained from *Pericarpium Citri Reticulatae* reportedly exhibit appreciable anti-asthmatic activity. The administration of alkaloids in animal models with histamine induced asthma, downregulated eosinophils expression in bronchoalveolar lavage fluid and serum along with notable attenuation of IgE, IL-4 and IL-5. The alkaloid demonstrated spasmolytic effects on acetylcholine chloride-induced contractions in the animal trachea [49]. Kim *et al*. 2019; identified natural bis-benzylisoquinoline alkaloids **19, 20** and **21** (Figure 2) form *stephania tetrandra*, which inhibited human coronavirus OC43 infection of MRC-5 human lung cells at its early stages.

Coronaviruses infect the respiratory tract thereby manifesting severe conditions such as bronchiolitis, and pneumonia [50]. The test alkaloids reportedly restricted the replication of human coronavirus OC43, restrained the expression of viral protein and virus-induced response of the host MRC-5 cells. Notably, the alkaloid **19** (Figure 2) activated the p38 Mitogen-Activated Protein Kinase (MAPK) pathway in the virus infected cells, which eventually improved their viability with minimal signs of cytotoxicity. The MRC-5 cells exposed to the test alkaloids showed negligible expression of proinflammatory cytokines, which are otherwise upregulated by the virus infection [51].

Deep-water sponges of the genus *Pakina* yield therapeutic alkaloid **22** (Figure 3), which displayed considerable bactericidal efficacy against *Mycobacterium tuberculosis* strain CDC1551. The test alkaloid Plakinamine P reportedly inhibited actively growing bacterial strain by 98 %, and dormant non-replicating bacteria by 67 %. The test alkaloid, being structurally similar to cholesterol and bearing undegradable side chains allegedly inhibits the cholesterol catabolism pathway in the host microbe, which is essential for its survival and for the persistence

of ensuing infection. In addition, the metabolic breakdown of test alkaloid by cholesterol degradation pathway yields toxic products fatal to the host microbe [52].

Coronaridine alkaloid **23** (Figure 3) isolated from *Tabernaemontana ternifolia* displayed marked antibacterial potency against *Mycobacterium tuberculosis* strain H37Rv with IC50 = 82.64 µg/ ml. The activity, however was lower than the commercial drug rifampicin (IC50 = 0.05 µg/ ml) [53]. Chen *et al*. 2017; isolated the alkaloid 'Talaramide A' (**24,** Figure 3) from *Talaromyces sp.* (strain HZ-YX1) and investigated its antimycobacterial potency by targeting mycobacterial protein kinase G (PknG), which plays a key role in the persistent localization of mycobacteria in macrophages. The alkaloid displayed significant inhibition of PknG with IC50 = 55 µM, thereby validating its potential for the treatment of chronic tuberculosis [54].

Besides several contemporary targets for capping tuberculosis, shikimate pathway represents the most recently identified means for the survival of mycobacterium. M*t*SK, one of the key enzymes associated with the shikimate pathway mediates the phosphorylation of shikimate substrate by abstraction of phosphate group from adenosine triphosphate (ATP) thereby producing shikimate-3-phosphate and adenosine diphosphate products. Manzamine alkaloids **25, 26** and **27** (Figure 3) isolated form Indo-Pacific sponge, *Acanthostrongylophora sp.* present mixed noncompetitive inhibition of M*t*SK enzyme. The kinetic profiling suggested that the inhibition of target enzyme occurred via two-step mechanism where the isomerization of preliminary EI complex results in highly unstable EI* intermediate. Notably, the alkaloid **25c** (Figure 3) due to 6-cyclohexamide substitution displayed superior potency compared to the peers with inhibition constant Ki = 0.06 µM [55]. Further research on marine sponge *Dendrilla nigra* for the identification of M*t*SK inhibitors led to the discovery of 3,4-diarylpyrrole alkaloids: Denigrin A, B and C (**28, 29** and **30**; Figure 3) [56].

Maarisit *et al*. 2017; identified the cyclic 3-alkyl pyridinium dimer alkaloids **31** (Figure 3) with antimycobacterial properties from the marine sponge *Haliclona sp.* [56]. Also referred to as cyclostellettamines when isolated from sponge *Pachychalina sp.*, the test alkaloids with longer alkyl chains connecting the pyridinium moieties exhibited excellent activity against *Mycobacterium Tuberculosis* strain H37Rv [57]. The precise mechanism of action for the test alkaloids **31** (Figure 3) is still under investigation. Besides the active mycobacterium, the non-replicating persistent *Mycobacterium tuberculosis* pathogen requires uninterrupted treatment for several months to prevent the relapse of disease [58].

The dormant mycobacterium requires hypoxic conditions for survival and displays considerable resistance against the representative drugs [59]. The marine sponge *Aaptos sp.* served as an excellent source for the isolation of aaptamine alkaloids **32 to 38** (Figure 3). Oxygen depletion instigated dormancy response of the mycobacterium in the form of resistance towards the antibiotic isoniazid served as the model for evaluating the anti-dormant mycobacterial efficacy of the test alkaloids. The test alkaloids displayed highly effective anti-dormant mycobacterial activity with IC50 in the range 1.5-6.25 µg/ ml. Further investigations suggested that the presence of carbonyl groups at C-3 and/ or C-9 position of the candidate alkaloids played a critical role in the expression of bioactivity against non-replicating dormant *Mycobacterium tuberculosis* [60]. These alkaloids formed the basis of identification of suitable pharmacophores for rationally designing the pharmaceuticals against dormant mycobacterium.

2. Flavonoids

Zhi *et al*. 2020; investigated the efficacy of flavonoids **39-46** (Figure 4) isolated form *Scutellaria baicalensis* against influenza A virus (IAV) induced acute lung injury (ALI). The inactive form of test flavonoids metabolized *in vivo* to anti-complimentary active metabolite aglycones **47-53**

(Figure 4) by the enzyme β-glucuronidase secreted by the epithelial cells, which demonstrated superior absorption into IAV-induced ALI animal models [61]. The infected animal models demonstrated a better metabolic transformation of the test flavonoids to active metabolites, with elevated levels in lungs and intestine, with higher content in the latter suggesting that the test flavonoids reach intestine first and then transformed to active metabolites before finally becoming a part of systemic circulation. The active metabolites **47-53** after reaching the lungs reportedly downregulate the levels of TNF-α, IL-6, monocyte chemotactic protein (MCP-1), while raising the levels of IL-10 and interferon-γ (IFN-γ), and considerably lowered the production of nitric oxide (NO) from lipopolysaccharide (LPS)-stimulated RAW264.7 cells thereby attenuating the activity of target virus [62].

Flavonoids **54-56** (Figure 4) extracted from *Houttuynia cordata* appreciably mitigated acute lung injury caused by H1N1 virus [63]. The animal models exposed to test flavonoids maintained the morphology of diseased lung microstructures, attenuated the penetration of proinflammatory factors MCP-1, IL-8, TNF-α, and malondialdehyde that play crucial role in the recruitment of macrophages and neutrophils at the site of stimulus [64]. However, the levels of interferon-β elevated, which played a key role in restricting the replication of virus [65]. In addition, the expression of TLR3/4/7 and level of NF-κ β p65 phosphorylation lowered in the lung tissues, which are associated with heightened activation and secretion of interferon-β [66]. Hence, the test flavonoids directed anti-inflammatory therapy served deliberated approach for countering IAV induced pathological processed manifesting acute lung injury. Reportedly, the flavonoids **54** and **56** (Figure 4) displayed enhanced biocidal potential against *Mycobacterium tuberculosis* H37Rv strain with IC50 = 6.25 and 25 µg/ ml respectively [67]. The biocidal potential of the test flavonoids proved better than the standard anti-TB drugs isoniazid and rifampicin.

Besides numerous efforts entailing anti-TB drug development, the emergence of drug-resistant mycobacterial strains necessitated the identification of novel drug targets by highly efficacious pharmacophores. MtPKnG, a protein kinase G produced by *Mycobacterium tuberculosis* represents serine/ threonine kinase enzyme, which prolongs the survival rate of the bacterium in host macrophages by preventing the phagosome-lysosome fusion [68]. The enzyme mediates phosphorylation of proteins associated with essential signal transduction pathways in bacteria and allegedly sustains the tuberculosis infection in the host [69]. Notably, the MtPKnG enzyme prompts anti-TB drug resistance in mycobacteria and serves as a key component for mycobacterial biofilms production. Hence, it forms a desirable target for anti-TB drug discovery against resistant mycobacteria.

Qasaymeh *et al*. 2019; reported bioactive flavonoids **57-59** (Figure 4) isolated from *Pelargonium sp.* with excellent binding affinity towards MtPKnG [70]. The *in silico* docking analysis confirmed the interactions of flavonoid **57** (Figure 4) with target enzyme MtPknG via H-bonding (<2.5 Å) with essential residues E233, E280, S239 and Q238. Similarly, the -OH groups present on B-ring of the test flavonoid **58** (Figure 4) showed H-bonding interaction with the residues K181, D293, and its flavone moiety interacted with Ala158 and Ile157 residues of the target enzyme. Nevertheless, the test flavonoid **59** (Figure 4) exhibited significant H-bonding interactions with residues K181 (2.498 Å), D293 (2.213 Å) and Q238 (2.278 Å) and hydrophobic interactions with the active site residues A158, I157, I165, I292 and M283 of the target MtPknG enzyme. These naturally occurring flavonoids hold tremendous potential for rationally designing pharmaceuticals and chemical therapeutics, essentially for targeting multidrug-resistant TB.

The drug resistance in microbes arises due to over-activity of the membrane bound efflux pumps that prevent the drug internalization in cells. The lack of clinically approved efflux pump

inhibitors further aggravate the disease pathogenesis. Polymethoxylated flavonoids **60-64** (Figure 5) reportedly reduced the rifampicin resistance and adversely affected the survival of *Mycobacterium tuberculosis.* Importantly, the bioactivity of anti-TB drug isoniazid enhanced in the presence of test flavonoids [71]. However, further investigations could not quantify the insight mechanism for the behavior of test flavonoids towards mycobacterium efflux pumps. Reportedly, the flavonoid **60** (Figure 5) considerably attenuated AHR, and reduced the expression of airway eosinophils and Th2 cytokines, whereas it amplified the levels of transforming growth factor-β1 (TGF-β1) in the bronchoalveolarlavage (BAL) fluids in OVA-sensitized animal models.

The administration of flavonoid **60** (Figure 5) also mitigated the collagen deposition in sub-epithelium, and suppressed goblet cell hyperplasia. Hence, the test flavonoid served as bradykinin antagonist and diminished the principal pathophysiological characteristics associated with allergic asthma [72]. Jeon *et al*. 2017; isolated flavonoid **65** (Figure 5), which exerted bactericidal effect on drug-resistant *mycobacterium tuberculosis* H37Rv strain. The test flavonoid reportedly inhibited the release of proinflammatory interleukins and attenuated the expression of TNF-α. The test flavonoid **65** (Figure 5) exhibits high affinity binding to M. tuberculosis β-ketoacyl acyl carrier protein synthase III (mtKASIII) enzyme via interactions of A-ring 2-OH and B-ring 4-OH groups of the flavonoid with N261 and C122 residues [73]. Importantly the open chain structure of phloretin permits membrane permeability against the mycobacterial cell wall, which protects the microbe from antibiotics and allows its persistence and proliferation in macrophages.

The flavonoids **66** and **67** (Figure 5) isolated from *Mosla chinensis* Maxim exerted inhibitory potential against H1N1 influenza virus mainly by downregulating the expression of the host TLR

signaling pathways [74]. In addition, the upregulation of critical factors (IL-6, TNF-α, IFNγ, and NO) and suppression of IL-2, SOD and cytokine GSH caused significant reduction of virus instigated inflammatory damage to lung tissues. Pawar *et al*. 2020, investigated the anti-tubercular activity of flavonoids **68** and **69** (Figure 5) by targeting glutamate racemase enzyme of the microbe associated with the synthesis of membrane peptidoglycans by transforming L-glutamate to D-glutamate.

The enzyme also plays a key role in DNA gyrase sequestration. The test flavonoids introduced deformations in the secondary and tertiary structure of the target enzyme by attenuating the helical contents, which manifested morphological changes in the microbial membrane. The interaction of test flavonoids with active site residues D12, C75, C185, and H187; present at the substrate binding site of glutamate racemase enzyme prompted its inhibition [75]. The flavonoids **70, 71** and **72** (Figure 5) proved highly efficacious for capping severe acute respiratory syndrome (SARS) caused by coronaviruses by inhibition of 3C-like proteases (3CLpro), responsible for autocleavage of viral polyproteins essential for viral propagation. The test flavonoids significantly blocked the enzyme activity by interacting effectively with the substrate-binding site via hydrophobic aromatic rings and hydrophilic –OH groups [76].

Mulberry root bark served as principal component for the isolation of prenylated flavonoid class 'sanggenols' **73-77** (Figure 5) bearing dual activity against influenza virus and *Streptococcus pneumoniae.* The prenylated flavonoids displayed high physiological tolerance while having an inhibitory potential superior to the standard drug olestamivir against the target neuraminidase (NA) enzyme, which sustains lethal synergy between the influenza virus and *S. pneumoniae* assisting the sustenance and longevity of the both [77].

In virus, the NA enzyme promotes reproduction and spread, whereas in the bacterium, NA enzyme facilitates the cleavage of sialic acid from glycoproteins present on the cell surface thereby affording receptors for attaching of microbe hence providing the host cell nutrients for further growth and colonization [78]. Hence, it makes a desirable target for attenuating the pathogenesis caused by Influenza virus and *S. pneumoniae*. These events allow the release of virus from infected cells and provides defense against representative drugs. The prenylated flavonoids effectively break this synergism thereby preventing the bacterial coinfection in the subjects with influenza [79].

3. Terpenes

Hirota *et al*. 2012, evaluated the potential of monoterpene limonene (**78**, Figure 6) in treating airway inflammation. Reportedly, limonene inhibits attenuates the allergic airway inflammation in *Dermatophagoides farina*-treated animal models, mainly by mitigating reactive oxygen species. The exposure to limonene significantly reduced the levels of interleukins-3/ 5, eotaxin, MCP-1, TGF-β in the bronchoalveolar lavages. In addition, the limonene administration abrogated gblet cell metaplasia, airway fibrosis, and thickness of the airway smooth muscles. These finding validated the candidature of limonene as prophylactic agent in asthma treatment [80].

Alavinezhad *et al*. 2017; investigated the therapeutic effect of carvacrol (**79**, Figure 6) on asthma subjects. The carvacrol exposure induced relaxant effect on the tracheal smooth muscles by reducing the total WBC, neutrophil, monocyte and eosinophil count in the blood and bronchoalveolar lavage fluid of the sensitized animal models. The relaxant effect of carvacrol occurs due to the significant attenuation of pro-inflammatory biometabolites in systemic circulation [81]. Boskabady *et al*. 2013; validated the preventive effect of carvacrol on tracheal

responsiveness in ovalbumin treated animal models. Interestingly, the treatment of animal models with carvacrol considerably lowered the levels of nitric oxide in serum, produced by endothelial nitric oxide synthase, which reportedly triggers plasma extravasation and lung edema [82]. Similarly, the higher levels of iNOS-derived nitric oxide raises vascular permeability, instigates mucus hypersecretion, and worsenes the inflammatory cell permeation, and epithelial cell damage that contribute to asthma pathology [83].

Wan *et al*. 2017; investigated the therapeutic effects of thymol (**80**, Figure 6) in animal models with LPS-induced acute lung injury. The LPS-challenged animals showed improved pathological changes in lung tissues on thymol exposure. Reportedly, the LPS-induced influx of the inflammatory cells and metabolites, interlukins and TNF-α attenuated in bronchoalveolar lavage fluid on thymol administration. In addition, thymol also restrained the LPS-mediated upsurge of MDO and MPS levels, and considerably lowered the activity of SOD thereby pausing the activation of NF-κB in the lungs [84]. These neutrophil localized enzymes primarily influence the adhesion and margination of neutrophils in the lung thereby causing severe lung injury.

Mohammadi *et al*. 2018; evaluated immunomodulatory effects of thymol in mitigating oxidative stress associated with asthma immunopathogenesis. Thymol-exposure attenuated the levels of 8-OHdG, an oxidative marker in asthma and carbonyl protein released by peroxidases from eosinophils in the airway passages, which elevates musine secretion, overexpresses cytokines and elevates apoptosis of epithelial cells lining airway passages. Reportedly, thymol affords considerable cytoprotective effect against the oxidative stress and moderately reinstates the defective trace element levels in asthma [85].

Gabri *et al*. 2019; studied the ameliorative effects of thymoquinone (**81**, Figure 6) on the LPS-induced pulmonary vascular damage. The protective effect appears because of the

downregulation of proinflammatory cytokines and interleukins in the presence of thymoquinone. In addition, thymoquinone administration attenuated the expression of NF-κB, TNFα, and IL-1β in the respiratory airways produced due to the LPS sensitization [86]. Thymoquinone also protects against lung damage caused by cigarette smoke by mitigating the expression of proinflammatory leukotrienes, prostaglandins, thromboxanes and importantly IL-1β, the principal biomarker cytokine in cigarette smoker's lung [87]. Su *et al*. 2016; evaluated the protective effects of thymoquinone in asthma animal models. Thymoquinone reportedly attenuated the expression of IL-4/5 and improved the expression of platelet endothelial cell adhesion molecule1 (CD31) and α-smooth muscle actinalpha (α-SMA) in ovalbumin-sensitized animals. In addition, thymoquinone deactivated VEGFR2-PI3K-Akt pathway and upregulated the expression of Slit glycoprotein-2 (Slit-2), which validates its anti-neoangiogenesis effect in asthma amelioration [88].

Qamar *et al*. 2008; investigated farnesol (**82**, Figure 6) for the effective amelioration of lung injury caused by cigarette smoke, known to cause pulmonary emphysema, COPD, and pulmonary fibrosis. The isoprenoids such as farnesol possesses excellent anti-nociceptive and chemopreventive potency and demonstrates protection against chronic lung inflammation, oxidative stress and lung injury caused by cigarette smoke intoxicants. The prophylactic treatment with farnesol showed lung-protective symptoms by lowering LDH levels, and lowered activity of reduced glutathione (GSH), glutathione reductase (GR), glutathione peroxidase (GPx) and catalase enzymes. The lowered H_2O_2 content in lung tissues further validated the cytoprotective effects of lung tissues against cigarette smoke [89]. Farnesol proved efficacious in the alleviation of benzopyrene-induced respiratory stress in animal models. Farnesol also sustained optimal levels of phospholipids and altered the catalytic activity of benzopyrene

enzymes NADPH–cytochrome P450 reductase, glutathione S-transferase (GST) and microsomal epoxide hydrolase (mEH) in the lung tissues of animal models. These findings suggested the protective role of farnesol against benzopyrene induced lung inflammation, edema, and epithelial damages in subject animals [90].

Gordien *et al*. 2009; reported the antimycobacterial activity of terpenes **83, 84** and **85** (Figure 6) isolated from *Juniperus communis* L. Reportedly, the terpene **84** (Figure 6) displayed enhanced activity against H37v strain of *Mycobacterium tuberculosis* with IC50 = 73.7 µM, and against the isoniazid-, streptomycin- and moxifloxacin-resistant strains with IC50 in the range 38.4-83.4 µM. The terpenes **83,** and **84** (Figure 6) demonstrated excellent activity against rifampicin-resistant variants with IC50 = 24 µM and 20.2 µM respectively. The terpene **85** (Figure 6) displayed noticeable inhibitory activity against *Mycobacterium aurum* with IC50 = 13.2 µM; however with a low selectivity index which indicated physiological toxicity [91].

Andrographolide (**86,** Figure 7) reportedly ameliorates LPS-induced acute lung injury by an effective downregulation of MAPK and NF-κB pathways, which regulate the production of inflammatory cytokines such as TNF-α and IL-6 in bronchoalveolar lavage fluid [92]. The anti-oxidative potency of andrographolide effectively restores the steroid sensitivity for blocking LPS-induced production of IL-27 and airway hyper-responsiveness. Moreover, andrographolide considerably restored the levels of nuclear HDAC2 protein and their total activity, whereas it contracted the total activity of histone acetyltransferase/HDAC in the animal lungs exposed to LPS/IFN-γ. These events occurred due to the suppression of phosphorylation of PI3K/Akt/HDAC2, and the upregulation of antioxidant transcription factor NF erythroid-2–related factor 2 level [93].

Sulaiman *et al*. 2018; presented the beneficial effects of andrographolide in offsetting toluene diisocyanate (TDI)-induced occupational asthma and aberrant distribution of E-cadherin in the airways. TDI represents the major cause of occupational asthma culminating 15 % of the global asthma deaths. The exposure of the respiratory airways to oxidants results in epithelial cell necrosis and functional impairment due to defective expression of adherens junction proteins such as E-cadherin and β-catenin. Hence, E-cadherin maintains epithelial barrier stability of the airway mucosa and allergic sensitization, which lowers in asthma condition thereby promoting the infiltration of oxidants via defected airway epithelium [94]. Andrographolide exposure maintained airway integrity by reversing the distribution of aberrant airway epithelial E-cadherin and β-catenin. In addition, it led to the attenuation of TNF-α induced production of oxidants and ROS via upregulation of Nrf2 through Akt phosphorylation [95].

Lampronti *et al*. 2017; reported therapeutic potential of β-sitosterol (**87**, Figure 7) extracted from *Nigella arvensis* L., in mitigating the expression of cytokine genes in cystic fibrosis epithelial cells lining bronchi. The test terpene significantly reduced the expression of neutrophilic chemokines IL-8, GRO-α, and GRO-β in LPS-sensitized human bronchial epithelial cells. These chemokines play a critical role in the recruitment of neutrophils in the lungs inflamed with cystic fibrosis. The investigations suggested that β-sitosterol partially inhibited LPS-triggered activation of Protein Kinase C isoform alpha, associated with transmembrane signaling for the activation of the expression of IL-8 gene in bronchial epithelial cells. Hence, β-sitosterol effectively mitigates the chronic lung inflammation in the patients with cystic fibrosis [96]. Further investigations suggested the attenuation of pulmonary fibrosis by β-sitosterol, by preventing the abnormal accumulation of extracellular matrix (ECM), manifesting deleterious effects to the alveolar epithelium resulting in epithelial–mesenchymal transition (EMT). β-

sitosterol, reportedly displayed anti-fibrotic effect while inhibiting EMT by downregulating the expression of transforming growth factor-β1 (TGF-β1). Notably, treatment with β-sitosterol convincingly blocked TGF-β1-induced protein expression of EMT markers, N-cadherin, vimentin, and E-cadherin [97].

Kim *et al*. 2012; studied effect of Ursolic acid (**88,** Figure 7) on ovalbumin-induced airway inflammation and airway hyper-responsiveness in animal asthma models. Ursolic acid displayed significant inhibition of airway inflammation via suppression of Th2 cytokines such as IL-5, IgE, and CCR3 expression [98]. Ursolic acid reportedly displays chemotherapeutic effect on COPD, and provides protection against cigarette smoke induced cell injury by suppressing the lung tumor metastasis [99]. The therapeutic effect of allergic asthma arises due to increase in the expression of PPARg and attenuated GATA-3 and STAT6 expression, resulting in a decrease of antigen-induced Penh, eosinophilia, lung inflammation, and the production of cytokines and antigen-specific IgE that play vital role in coordinating and intensifying the allergic inflammation in asthma [100]. Reportedly, the treatment with ursolic acid alleviates emphysema instigated by cigarette smoke by PERK pathway, as well as Nrf2 pathway [101]. The activation of PERK discourages protein synthesis via phosphorylation of eukaryotic translation initiator factor, thereby causing a selective translation of ATF4, which controls the expression of critical apoptotic association genes.

Nuclear erythroid-related factor 2 (Nrf2) represents a transcription factor regulating several antioxidant and detoxification genes [102]. Nrf2 signaling pathway plays a critical role in cigarette smoke-induced emphysema. Reportedly, ursolic acid demonstrates protective effects against cigarette smoke-induced emphysema through PERK andNrf2 signaling pathway. Further investigations on beneficial pulmonary effects of ursolic acid suggested that the terpene

effectively alleviates cigarette smoke induced emphysema and airway remodeling involving unfolded protein response (UPR) pathways by suppression of ERS-associated apoptosis, and downregulation of IGF1, TGF-β1, and p-Smad2/3 expression [103, 104]. These factors mediate bronchial epithelial and muscle cell regeneration in COPD patients through effects on airway vessel remodeling and muscle atrophy.

Lee *et al*. 2010; appraised theanti-asthma potency of Betulinic acid (**89,** Figure 7) isolated form *Forsythia viridissima*. The terpene successfully paused the activity of histamine and phospholipase A2 in bronchoalveolar lavage fluid at a 12.5 mg/ kg dose. The activity of eosinophil peroxide (EPO) and eosinophil recruitment lowered at a dose of 25 mg/ kg. These metabolites act as the precursors of chronic inflammation in the airway passages [105]. Ekuadzi *et al*. 2017; further validated the potency of betulinic acid for the treatment of respiratory ailments, chiefly the carrageenan induced lung inflammation in animal models by successful inhibition of the production of proinflammatory chemokines and cytokines [106].

Jiang *et al*. 2017; reported the beneficial effects of Oridonin (**90,** Figure 7) for capping acute respiratory distress syndrome (ARDS) in animal models. The test terpene notably mitigates the expression of inflammatory metabolites and factors such as TNF-α, IL-6, and NF-κB p56. Conversely, the expression of Iκ-B α augmented in lung tissues and bronchoalveolar lavage fluid [107]. Wang *et al*. 2016; further verified the protective effects of oridonin by studying its anti-asthma potential in ovalbumin-sensitized animal models. Reportedly, oridonin sustains Th1/Th2 cytokines balance in sensitized animal models and demonstrated anti-asthmatic effects in acute asthma model [108].

4. Clinical Significance

Structurally diverse, plant derived natural products bear a privileged status in rational designing of commercially successful medicines. The identification of plant based natural molecules with therapeutic properties prompted systemic efforts to explore and commercially exploit the nature-derived drugs for countering clinical intricacies associated with the chronic diseases [109]. The natural product based drugs present considerable commercial representation under various brand names, as well as a significant number of candidate molecules in clinical trials [110]. However, the nature-derived molecules in chronic respiratory diseases present only a limited clinical profile, with even fewer molecules in commercial scaling [111].

A randomized controlled trial conducted in 60 patients with moderate to severe asthma suggested the safety and efficacy of *Squill oxymel* (a popular Iranian medicine obtained from *Drimia maritima*). *Squill oxymel* was able to significantly increases the force expiratory volume (FEV) 1 liter, FEV1%, FEV1/force vital capacity (FVC%), and maximal mid expiratory flow (MEF) as compared to placebo. There was a remarkable improvement in symptoms, activity, and total score in the patients administered *Squill Oxymel* but not in the placebo group. Moreover, there was no serious adverse observed except minor nausea and vomiting reported in five patients in *Squill oxymel* group. This trail showed a strong potential of *Squill Oxymel* in terms of safety and efficacy for asthma patient [112]. Another double-blind randomized controlled clinical trial involving 85 asthma patients investigated whether plant stanol ester improves immune function in those patients. The effect of plant stanol added in soy-based yogurts in half of the patient on comparison with remaining half receiving control yogurt (placebo group) suggested considerable therapeutic results. It was observed that patients receiving plant based stanol ester group showed increased antibody titres against hepatitis A virus after 3 week [19% ($P = 0.037$)] and 4 wk [22%

(P = 0.030)] of vaccination. Likewise, there was a marked depletion in plasma total IgE, TNF-α, IL-1β in plant-stanol ester group compared to placebo control. Furthermore, a correlation appeared between the increase in serum plant-stanol concentrations and decrease in IL-13 concentrations as well as Th1 switch in the Th1/Th2 balance [113]. The alkaloids such as theophylline, lobeline, and narceine have been commercialized as adenovasin, citotal, and peneraj respectively for relieving chronic symptoms associated with asthma, however several molecules fail to clear the clinical trials prior to successful commercialization [114, 115].

Sulforaphane is a derivative of broccoli and commonly found in cruciferous vegetables. A phase 2 randomized trail conducted in 89 COPD patients were given either placebo or 25 μmoles or 150 μmoles of sulforaphane orally for 4 wks. The changes in nuclear factor erythroid-2 related factor 2 (Nrf2) target gene expression in bronchial epithelial cells and alveolar macrophages as well as measurement of oxidative damage, airway inflammation, and pulmonary function tests were tested. However, sulforaphane did not induce the Nrf2 target gene expression and no significant anti-oxidant and anti-inflammatory activity appeared as compared to placebo control [116]. Thyme herb, ivy leaves and primose roots exhibit beneficial effects against acute bronchitis and productive cough [117].

Gruenwald et al., 2005 and Kemmerich B. 2007 separately conducted a double-blind randomized control trial to study the efficacy and tolerability of thyme herb and primose root combination therapy In Gruenwald et al., 2005 study, the combination therapy was administered as 1ml orally in 75 outpatient suffering with bronchitis while remaining 75 patients were given placebo. The combination therapy was effective in significantly reducing the bronchitis severity score leading to more patients with symptom free in combination therapy as compared to placebo group at the end of study. Both groups tolerate the treatment very well as there was no serious adverse events

observed [118]. Similarly in Kemmerich B study, 183 patients with acute bronchitis were given with 1 tablet of thyme-primose combination thrice a day for 11 days and the efficacy was compared with placebo (N= 178 patients). There was a mean reduction of 67.1% of coughing fits in combination therapy group compared to 51.3% in placebo group on day 7 to 9. The combination therapy reduces the coughing fits to 50% two days earlier than placebo group. Further, no severe adverse events appeared in both groups, which concludes the well tolerability of thyme-primose combination therapy [119].

Kemmerich B et al. 2006 further reported in another trial investigating the efficacy and tolerability of thyme herb and ivy leaves in acute bronchitis patient. Similarly, the safety and efficacy of alcoholic extract of Echinacea purpurea herb (95%) and root (5%) in a large population (755 healthy volunteer) over 4 month's duration demonstrated significant therapeutic effects. The efficacy of extract to prevent the common cold episode when compared with placebo group showed beneficial activity against common cold by reducing the total number of cold episode as well as cumulated episode days. Furthermore, the extract was able to prevent enveloped virus infection. Regarding safety issue, 9% of participants in Echinacea extract treated group and 10% in placebo group showed adverse effect concluding the safety of Echinacea as non-inferior to placebo. The clinical trials evaluating the safety and efficacy of various natural product compounds in chronic respiratory disease are scarce. The limited clinical trials with few promising natural moieties need further validation with multiple evidence [120].

In Table 2, we present the clinical studies on natural product-based molecules for countering the chronic respiratory disorders in human subjects.

5. Conclusion and Future Perspectives

Chronic respiratory disorders mainly arise due to the bronchial and pulmonary inflammation arising due to the heightened innate response causing an upsurge of proinflammatory metabolites, and over activity of enzyme such as cyclooxygenases, and lipoxygenases. The inhalation of toxicants manifests the recruitment of inflammatory cells in the bronchial and alveolar mucosa. The perseverance of nonspecific macrophages and adaptive T-lymphocytes even after the prolonged stimuli cassation inappropriately instigates the memory cells of adaptive immunity, an event further maintained by dendritic cells, which also induce remodeling of lung tissue. In addition, the oxidative stress and disturbance in protease/ antiprotease balance deter the beneficial effects of corticosteroids in managing airway inflammation.

The ensuing effects include increased thickness of the bronchial wall leading to narrowing of the lumen, increased tone of bronchial smooth muscle leading to loss of elasticity and mucus oversecretion, proliferation of fibroblasts, detrimental extracellular matrix, and apoptosis in the endothelial cells. The involvement of multiple regulatory pathways in mediating respiratory disorders necessitates the development of multi-targeting medications. The practice of polypharmacy holds considerable potential for effectively managing the composite pulmonary maladies, considering the patient compliance. Mucoactive drugs such as ‘erdosteine’ combat broncho-obstructive symptoms by reinstating mucociliary clearance.

Notably, erdosteine displays significant antibiotic effect thereby attenuating the bacterial load during the respiratory distress. Similarly, the pulmonary disorders caused by multidrug-resistant microbes such as *mycobacterium tuberculosis*, and *streptococcus pneumoniae* requires innovative pharmaceuticals with multifarious targeting potential. Reportedly, the isoniazid monotherapy or rifampicin or pyrazinamide bitherapy proved inadequate for the disease

management and resulted in its recurrent cycles. Hence, the recommended anti-TB regimen suggests polypharmacy as preliminary combination therapy of rifampin, isoniazid, pyrazinamide, ethambutol, and pyridoxine to prevent the recurrence of disease. Nevertheless, the amenability of the subjects to the combination of drugs, and the probability of microbial susceptibility to the administered doses raises compulsion for the identification of physiologically tolerable, novel pharmacophores for which the natural products present an ideal profile.

Acknowledgements

Meenu is supported by the Graduate School of Health and University of Technology Sydney (International Research Training Program Scholarship (IRTP)).

Kamal Dua is supported by a project grant from Rebecca L. Cooper Medical Research Foundation and Sydney Partnership for Health, Education, Research and Enterprise (SPHERE) for the TRIPLE I CAG Secondment/ Exchange grant.

Philip M. Hansbro is supported by a fellowship from the National Health and Medical Research Council of Australia (NHMRC #1079187).

Keshav Raj Paudel is supported by a fellowship from Prevent Cancer Foundation (PCF)/International Association for the Study of Lung Cancer (IASLC).

Declaration of Interest: None

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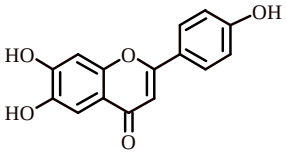
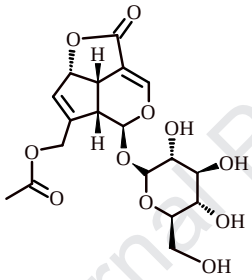
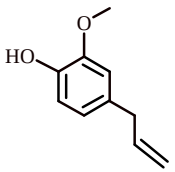
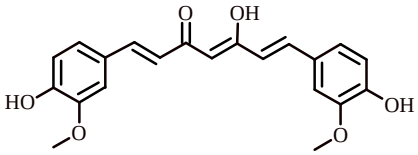
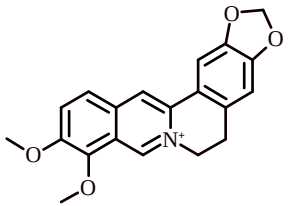
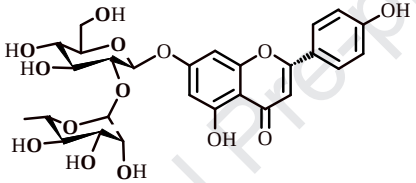
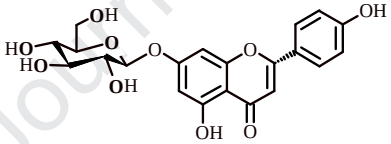
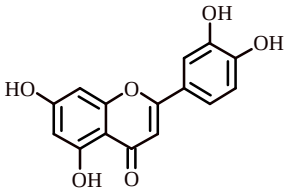
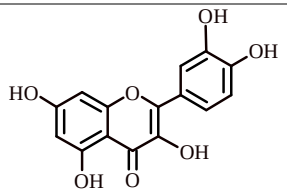
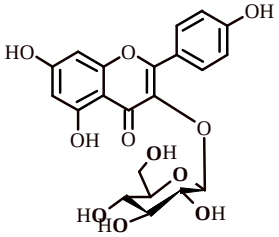
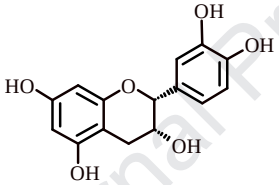
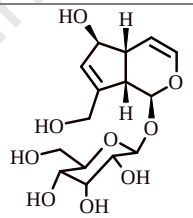
Table 1: Natural products showing effect in respiratory disorders

S.No.	Natural product	Nature	Chemical structure	Pharmacological/ Mechanism of action	Ref.
1.	Apigenin	Flavonoid		• Anti-inflammatory via reducing the levels of interleukin (IL)-6, TNF- α and IL-17A • Anticarcinogenic • Antioxidant	[26]
2.	Asperulosid e	Iridoid glycoside		• Anti-inflammatory via inhibition of MAPK and NF-κB signaling	[27]
3.	Eugenol	Terpenoid		• Ameliorate oxidative stress, • Anti-inflammatory via downregulation of TNF-α and IL-6 levels	[28]
4.	Curcumin	Alkaloid		• Ameliorates allergic airway inflammation and hyper-responsiveness by inhibiting the activation of NF-κB signalling pathway	[29]

5.	Berberine	Alkaloid		• Decrease in pro-inflammatory cytokine (TNF-α and IL-6) levels, • Inhibit NF-κB signalling pathway, • Increase the level of antioxidants in the body, • Reduces viability of cancerous cells	[30]
6.	Naringin	Flavanone glycoside		• Antioxidant, • Anti-inflammatory, Anti-apoptotic, • Anti-carcinogenic properties	[31]
7.	Naringenin	Flavonoid		• Anti-inflammatory via inhibition of pulmonary IkappaBalpha degradation and NF-kappa-B DNA-binding activity	[32]
8.	Luteolin	Flavone		• Inhibit MAPK and NF κB pathway • Reduces neutrophil inflammation • Inhibits LPS-induced TNF-α, interleukin-6. • Inhibits nitric oxide production in macrophages	[33]

9.	Quercetin	Flavonoid		• inhibits serum necrosis factor α, IL-1β, IL-6, nitric oxide (NO), IL-10 • Show anti-inflammatory and antioxidant properties	[34]
10.	Kaempferol glycoside	Flavonoid		• Suppress MAPKs and NF-κB signaling pathway	[35]
11.	Epicatechin	Flavonol		• Inhibits TNF-α expression • Inhibits proliferation of tumor cells and promotes cell death by apoptosis	[36]
12.	Picroside II	Iridoid glycoside		• Anti-inflammatory effect via suppressing neutrophilic lung inflammation	[37]

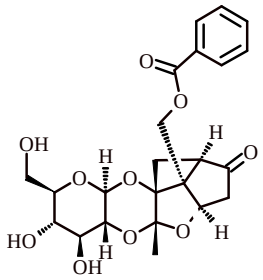
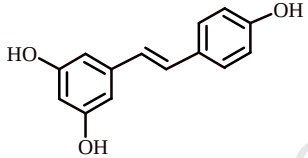
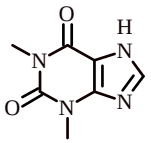
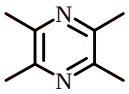
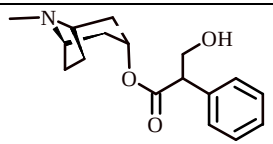
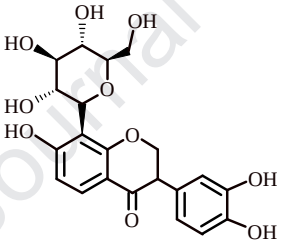
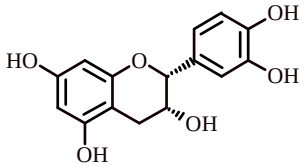
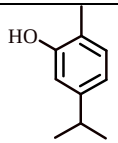
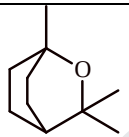
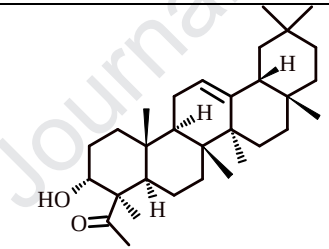
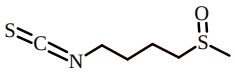
13.	Lactiflorin	Monoterpene glycoside		• Suppress the production of NO synthase and ROS	[38]
14.	Resveratrol	Polyphenolic compound		• Sensitize tumor cells to chemotherapeutic agents by modulating multiple cell signalling molecules	[39]

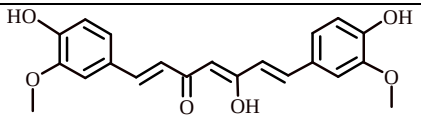
Table 2: Clinically significant natural product based molecules in attenuating respiratory disorders

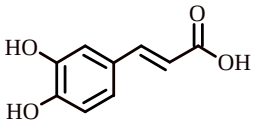
Alkaloids

Sr. No	Compound	Source	Structure	Application	Mechanism	Ref.
1.	Theophylline	*Camellia sinensis* and *Theobroma cacao*		Inhibits the Exacerbations in human subjects with COPD, bronchodilation	Suppression of inflammatory genes by enhanced HDAC activation	[121, 122]

2.	Ligustrazine	*Ligusticum wallichii Rhizome, Curcuma aromatica Salisb, Jatropha podagrica Hook*		Treatment of pulmonary arterial hypertension (PAH) in human subjects	Upregulates levels of NO and downregulates ET-1; lowers mPAP levels.	[123, 124]
3.	Atropine	Family *Solanaceae*		Relieves asthma chronic bronchitis	Reduction in sputum volume	[125]
		Flavonoids				
4.	Puerarin	*Pueraria montana var. lobata*		Treatment of pulmonary arterial hypertension (PAH) in human subjects	Restrains pulmonary vascular remodeling	[126]
	Procyanidin	*Cocoa*		Relieves oxidant stress in human subjects	Trigger Nrf2 activity	[127]

			Terpenoids			
5.	Carvacrol	*Origanum vulgare*		Therapeutic effect on asthma in human subjects	Downregulation of inflammatory cells, and high-sensitivity C-reactive protein (hs-CRP)	[128]
6.	Eukalyptol	*Eucalyptus sp.*		Relieves bronchial asthma and rhinosinusitis in human subjects	Mucolytic agent in upper and lower airway passages	[129, 130]
7.	Boswellic acid	*Boswellia serrata*		Alleviates symptoms of asthma in human subjects	Deactivation of lipoxygenase pathway	[131]
			Miscellaneous			
8.	Sulforaphane	*cruciferous vegetables*		Attenuates inflammatory effects of oxidative stress in respiratory passages in	Induces the expression of mucosal Phase II enzymes in the upper airway	[132]

				human subjects	passage	
9.	Curcumin	*Zingiberaceae family*		Prevention of deleterious cardiovascular events in COPD human subjects	Decreased the atherosclerotic AT-LDL levels, resulting in prevention of possible cardiovascular disorders in COPD subjects	[133]
10.	Pycnogenol	*Pinus pinaster*	*Complex antioxidant compounds*	Relieves asthma inflammation in human subjects	Inactivation of NF-κB and attenuation of MMP-9 secretion	[134]
11.	Linoleic acid	*Vegetable oils*	*Polyunsaturated fatty acid*	Improves the airway hyper□reactivity in asthma human subjects	Downregulation of stimulated TNF-α	[135, 136, 137]

12.	Caffeic acid	*Eucalyptus globulus*		Significant inhibition in the incidence and severity of nocturnal attacks, improvement of ventilatory functions in asthma human subjects	Reduction in pro□ inflammatory factors (TNF)□α, ICAM□1, IL□6, IL□8, prostaglandins E2 and F2α and leukotriene D4; upsurge in IL□10. The levels of	[138]

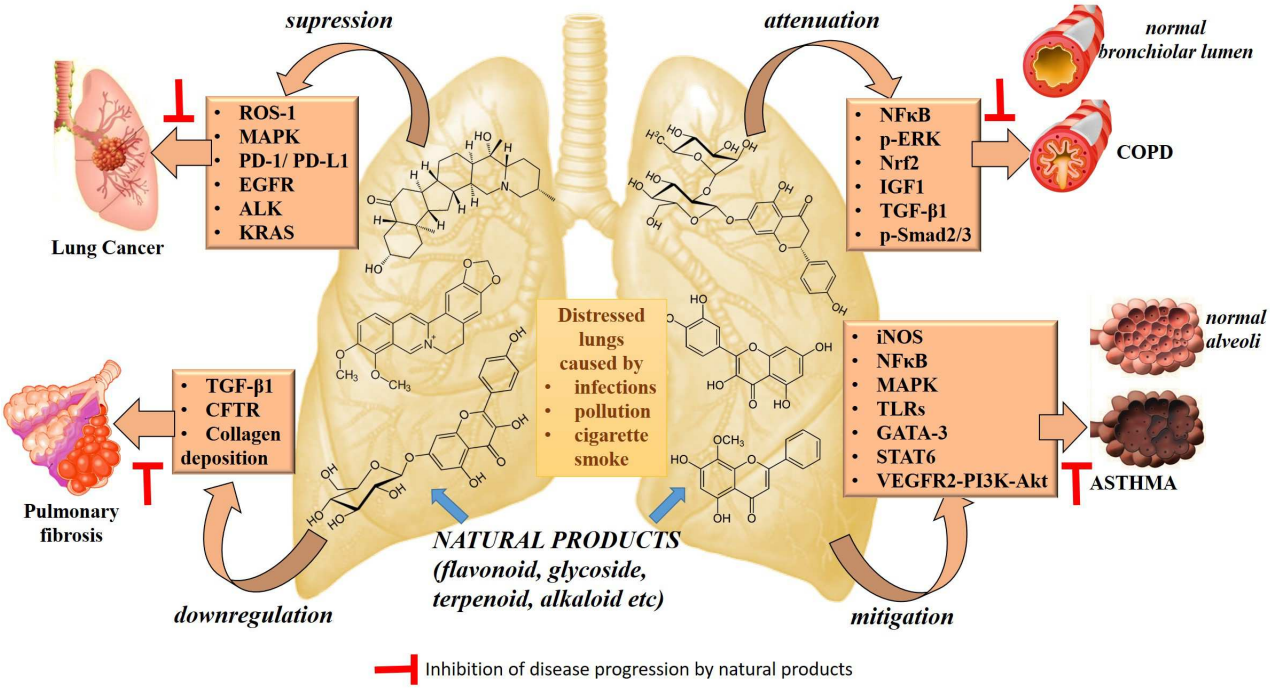


Figure 1. Natural products targeting different cell signaling pathway

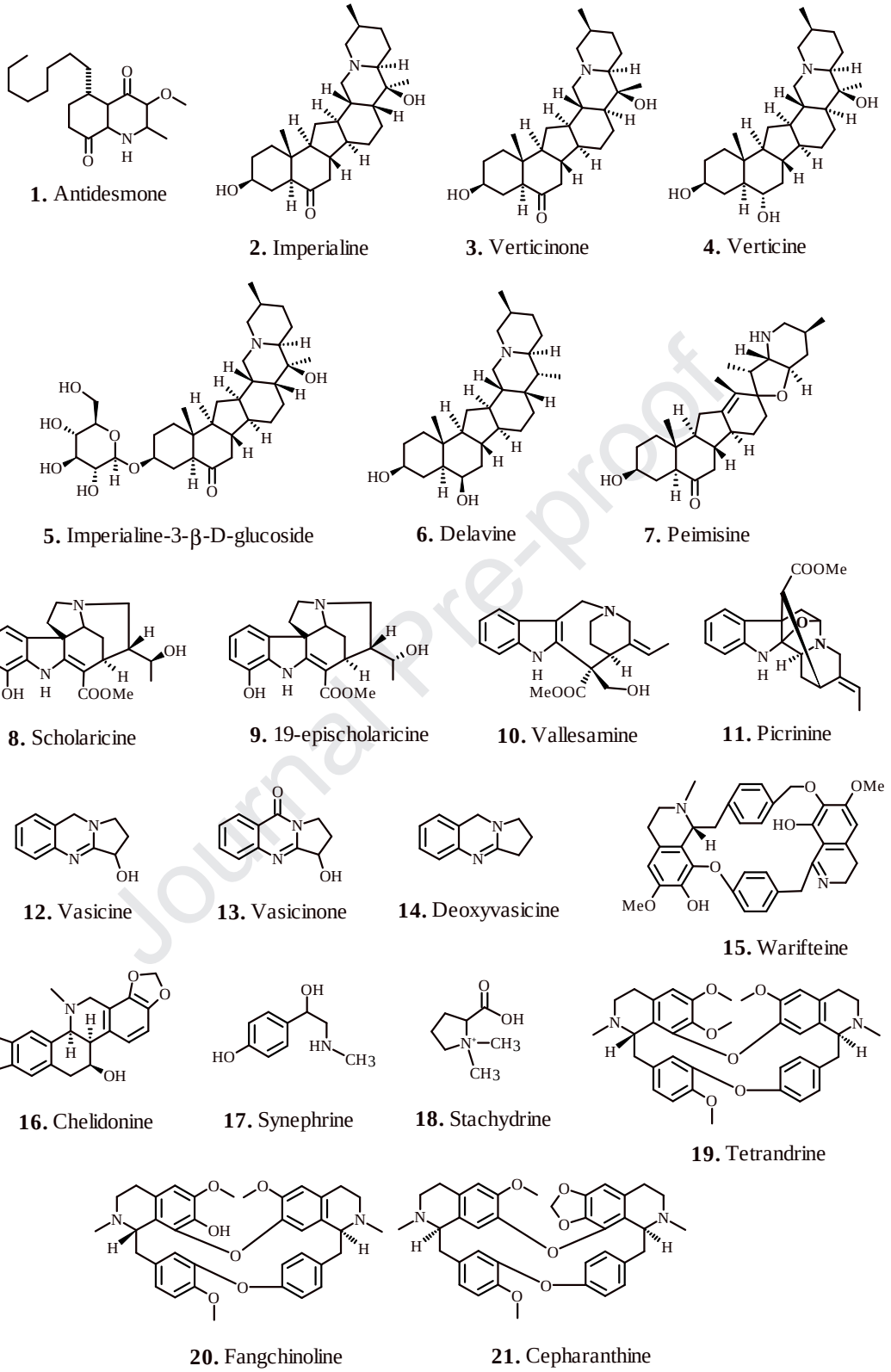
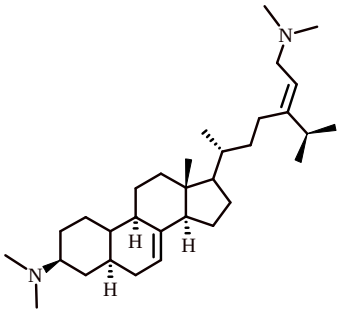
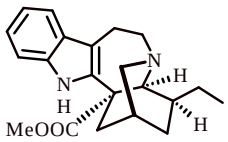


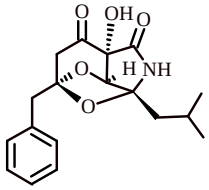
Figure 2. Alkaloid based medicinal compounds for the treatment of respiratory disorders



22. Plakinamine P

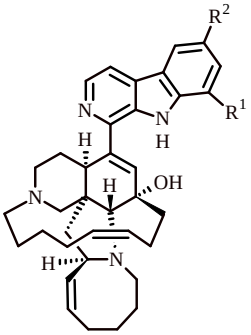


23. Coronaridine



24. Talaramide A

MANZAMINE ALKALOIDS (25-27)

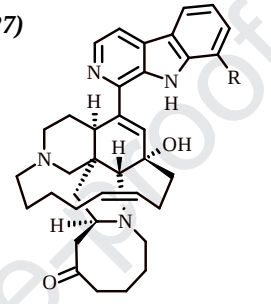


25.

a. $R^1 = R^2 = H$ (Manzamine A)

b. R^1, R^2 = OH, H (8-OH-manzamine A)

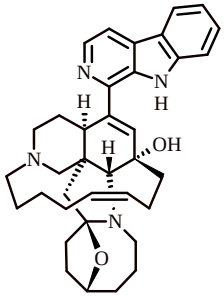
c. R^1, R^2 = H, cyclohexamide (8-cyclohexamido-manzamine A)



26.

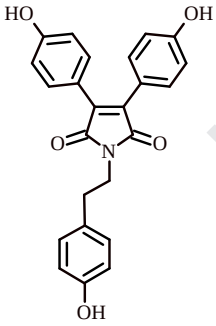
a. R = H (Manzamine E)

b. R = OH (Manzamine F)

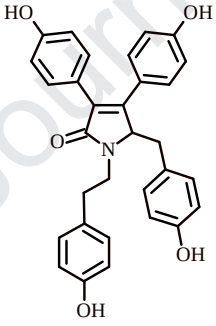


27. 6-deoxy manzamine X

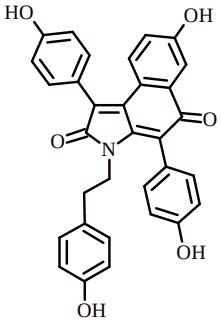
DENIGRINS A-C (28-30)



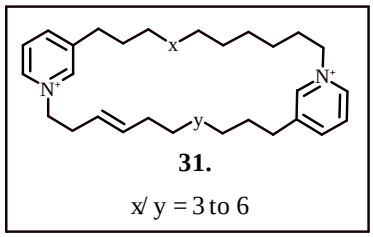
28. Denigrin A



29. Denigrin B

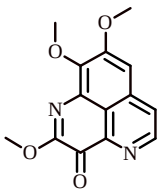


30. Denigrin C

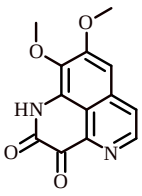


31. x/ y = 3 to 6

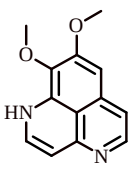
AAPTAMINES (32-38)



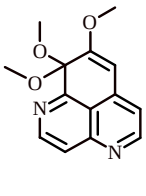
32.



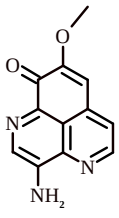
33.



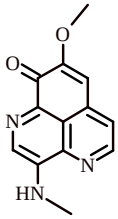
34.



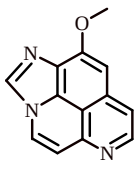
35.



36.



37.



38.

Figure 3. Alkaloid based medicinal compounds for the treatment of tuberculosis

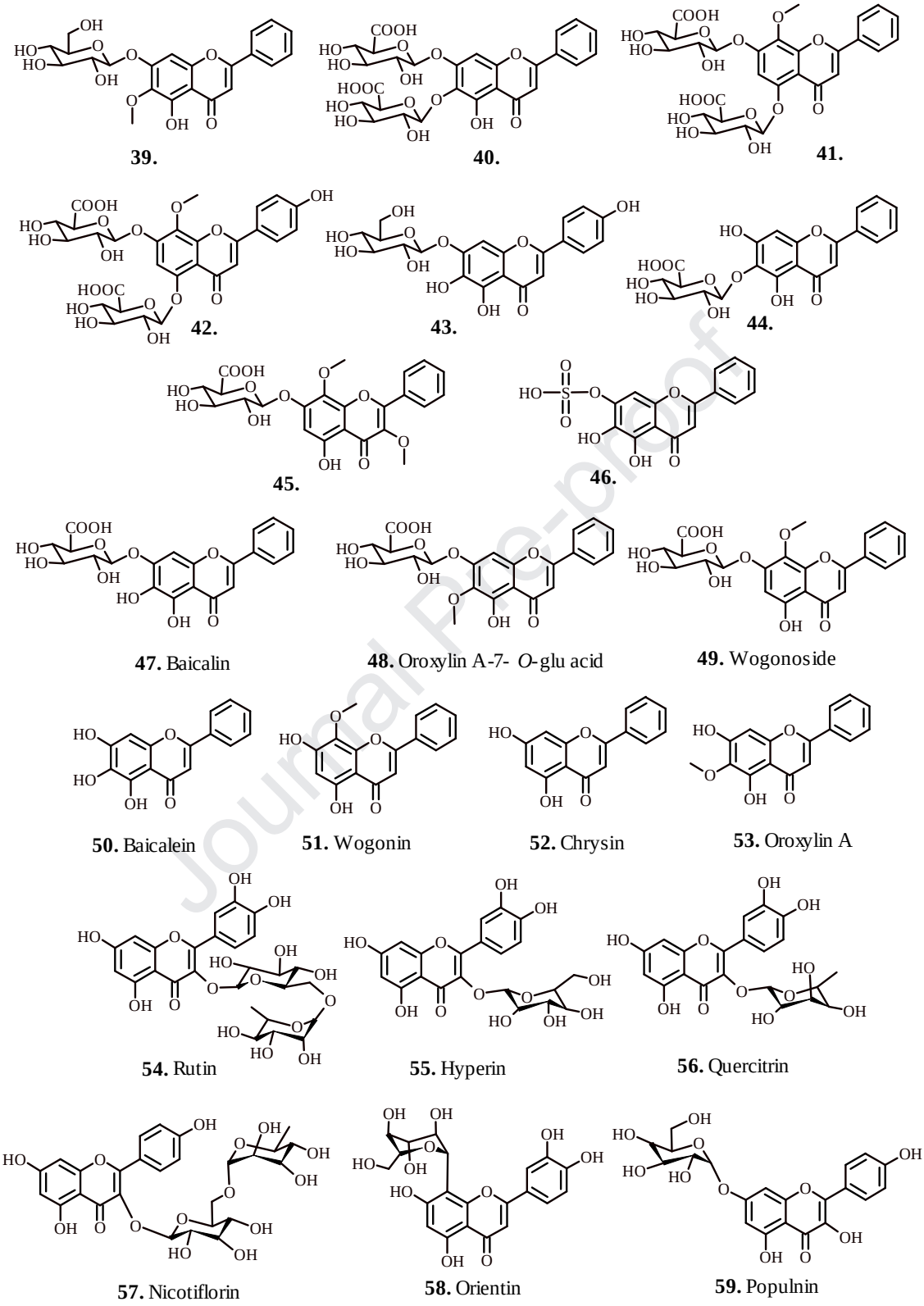
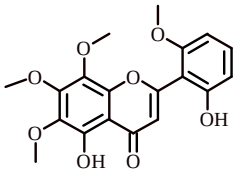
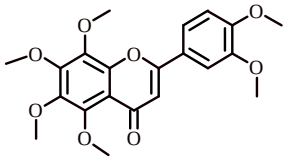


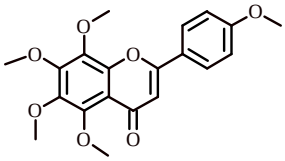
Figure 4. Flavonoids for the treatment of respiratory disorders (a)



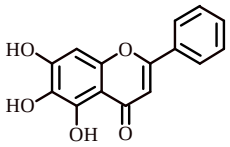
60. Skullcapflavone II



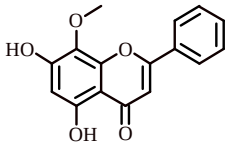
61. Nobiletin



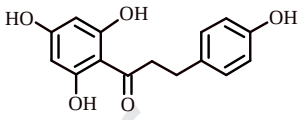
62. Tangeretin



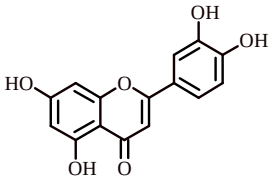
63. Baicalein



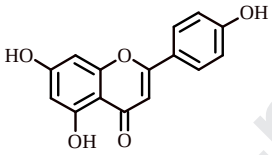
64. Wogonin



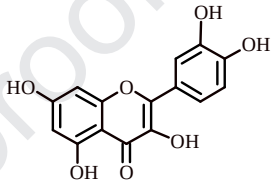
65. Phloretin



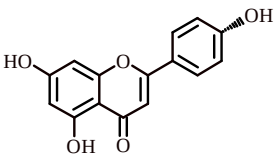
66. Luteolin



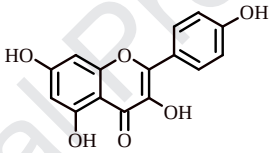
67. Apigenin



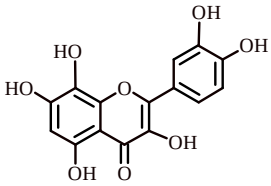
68. Quercetin



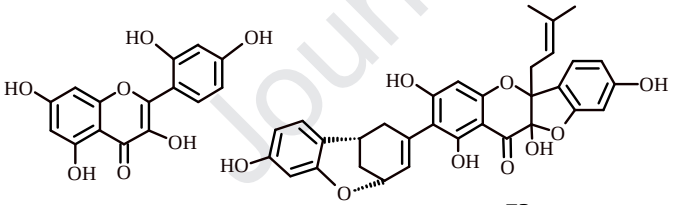
69. Naringenin



70. Kaempferol

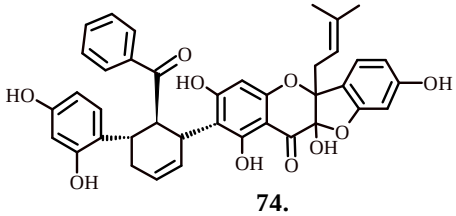


71. Herbacetin



72. Morin

73.



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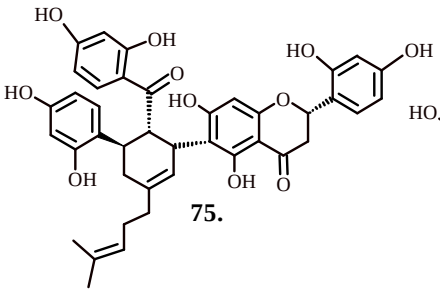

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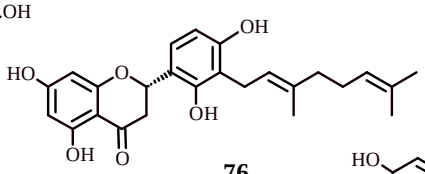

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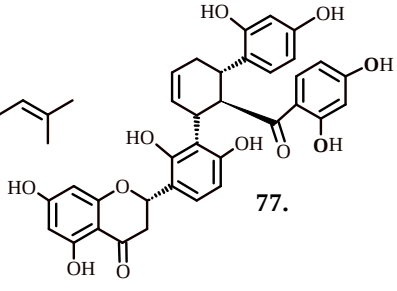
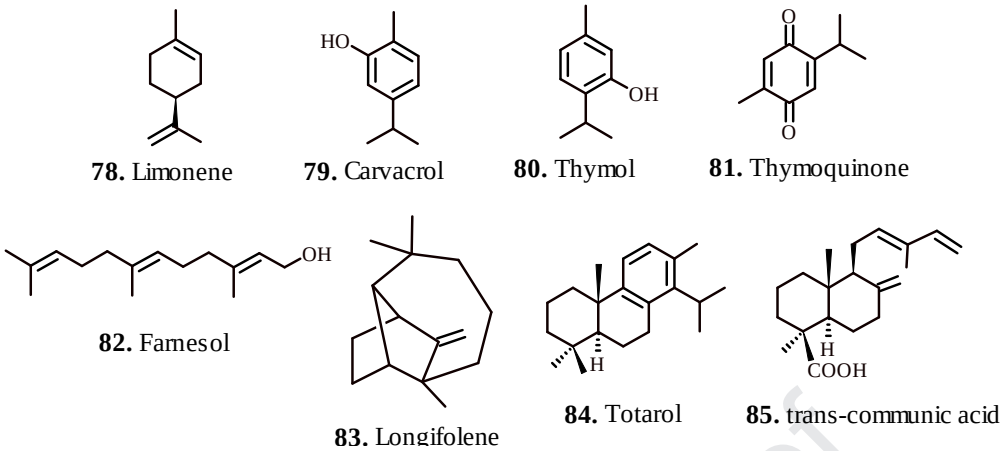


77.

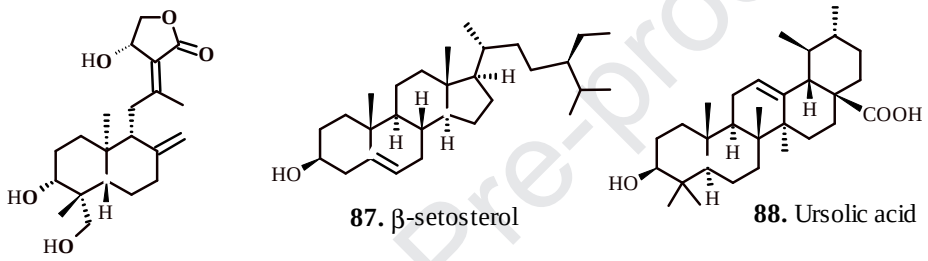
Figure 5. Flavonoids for the treatment of respiratory disorders (b)



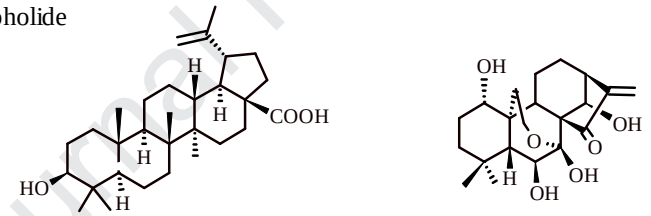
78. Limonene **79.** Carvacrol **80.** Thymol **81.** Thymoquinone

82. Farnesol **83.** Longifolene **84.** Totarol **85.** trans-communic acid

Figure 6. Important terpenes for the treatment of respiratory disorders (a)



86. Andrographolide **87.** β-setosterol **88.** Ursolic acid



89. Betulinic acid **90.** Oridonin

Figure 7. Important terpenes for the treatment of respiratory disorders (b)

Highlights

- Plant derived therapeutics for managing chronic respiratory disorders.
- Activity of natural product based molecules on key regulatory pathways of COPD.
- Preclinical evidence for the efficacy of natural product moieties.
- Clinical significance of plant derived molecules in pulmonary distress.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: